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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,840	LEADLAY ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,23-25,29,30 and 43-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,23-25,29,30 and 43-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on April 11, 2003), Applicants filed an amendment and response received on September 10, 2003. Said amendments cancelled Claims 16-19, 21-22, and 26-28, amended Claims 20, 29, 30, and 43, and added new Claims 44-63. Thus, Claims 20, 23-25, 29, 30, and 43-63 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for International Application No. PCT/GB99/02044 filed on June 29, 1999 and UK Application No. 9814066.4 filed on June 29, 1998.

Drawings

3. New drawings of Figures 2-7 have been received.

Compliance with the Sequence Rules

4. By virtue of Applicants' amendment to the specification, the instant application now fully complies with the sequence rules.

Withdrawn - Objections to the Specification

5. Previous objection to the specification for informalities on pages 35, 45, 51, and 56, concerning stray marks on the chemical structure is withdrawn by virtue of Applicants' amendment.

Maintained or New - Objections to the Specification

6. (New) The specification is objected to in its description of the figures. Figures 3A and 3B must both be described in the Brief Description of the Drawings. Also, in the description of Figure 4, no mention of the arrow (located in Figure 4B) is found, thus, its presence is unclear. Correction is required.

Withdrawn - Claim Objections

7. Previous objection to Claim 28 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicant's cancellation of said claim.

New or Maintained – Claim Objections

8. (New) Claims 43, 46, and 54 are objected to for a typographical error. In lines 8 or 9, the word "molecules" is used instead of ---modules--- that is the appropriate term. Correction is required.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

9. Previous rejections of Claim 16 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicants' cancellation of said claim.

10. Previous rejection of Claims 16-30 and 38 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "loading module" is withdrawn by virtue of Applicants' amendment.

11. Previous rejection of Claims 19 and 39 under 35 U.S.C. § 112, second paragraph, as being indefinite for the option of having a CLF domain or a ketosynthase β domain is withdrawn by virtue of Applicants' cancellation of said claims.

12. Previous rejection of Claim 22 under 35 U.S.C. § 112, second paragraph, as being indefinite for the nature of the KS^Q-AT^Q pair is withdrawn by virtue of Applicant's cancellation of said claim.

13. Previous rejection of Claim 29 under 35 U.S.C. § 112, second paragraph, as being indefinite for the antecedent basis of "the KSq domain" is withdrawn by virtue of Applicants' amendment.

14. Previous rejection of Claim 30 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "variants of rifamycin, etc." is withdrawn by virtue of Applicants' amendment.

15. Previous rejection of Claims 38-40 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "wherein at least part of the first extension module is heterologous to said loading module or at least a domain thereof" is withdrawn by virtue of Applicants' cancellation of said claims.

16. Previous rejection of Claims 39, 40, and 43 under 35 U.S.C. § 112, second paragraph, as being indefinite for the decarboxylating portion of the loading module is withdrawn by virtue of Applicant's amendment.

17. Previous rejection of Claims 39, 40, and 43 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "engineered domains" is withdrawn by virtue of Applicant's amendment.

New or Maintained - Claim Rejections - 35 U.S.C. § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. (New) Claims 20, 23-25, 29, 30, and 43-63 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 43, 46, and 54, the independent "base" claims, are generally narrative and indefinite, failing to conform to current U.S. practice. Moreover, they contain repetitive limitations and arduous punctuation; use of indents and appropriate, separate "wherein" clauses are encouraged as follows:

46. A type I polyketide synthase which produces a polyketide and which comprises a loading module and a plurality of extension modules, wherein said loading module is

a) not naturally associated with at least the first of said extension modules, and
b) of the form (natural-KSq)-(AT)-(ACP), wherein
    i. ACP represents an acyl carrier protein,
    ii. AT represents an acyltransferase domain adapted to load a starter unit provided by the KSq domain, and
    iii. KSq represents a naturally-occurring ketosynthase domain which effects decarboxylation of the starter unit;

    wherein said starter unit is an optionally substituted malonyl and wherein said KSq domain differs from a KS domain of an extension module by having a glutamine residue in place of the cysteine in the active site;

wherein the polyketide produced is other than a 14-membered macrolide having a 13-methyl group due to incorporation of an unsubstituted acetate starter unit.

19. (New) Claims 20, 23-25, 29, 30, and 43-63 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the independent claims, the use of the term "residue" to describe anything other than an amino acid residue is confusing and repugnant to the common definition in the art. This description is particularly confusing considering the later requirements of changing cysteine residues to glutamine residues. The Examiner suggests the term ---moiety---. Clarification is required.

20. (New) Claims 20, 23-25, 30, and 43-63 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The nature of the loading module is unclear. In Claims 43, 46, and 54, the phrase "wherein at least the first of said extension molecules [modules] is not naturally associated with **a** loading module that effects decarboxylation of an optionally substituted malonyl" (emphasis added) is unclear. Firstly, it seems that the loading module referred to should be ---said loading module--- since virtually all loading modules in nature ("**a** loading module", emphasis added) effect decarboxylation of an optionally substituted malonyl and then, this limitation would require that the extension module not be naturally associated with virtually any loading modules. This seems an unlikely scenario in light of the specification.

Assuming, then, that the claims should be drawn to a hybrid PKS "wherein at least the first of said extension modules is not naturally associated with said loading module that effects decarboxylation of an optionally substituted malonyl"; must the loading module – that is (natural-KSq)-(AT)-(ACP) all be naturally associated with each other? If not, which domain,

since they are treated as a group under the name "loading module," governs so as not to be naturally associated with the extension modules?

In the examples in the specification, most of the examples are drawn to using entire loading modules from a particular source (pPFL43 uses the monensin loading module and DEBS extension modules, pPFL42 uses the tylosin loading module and DEBS extension modules, and pPFL44 uses the spiramycin loading module and DEBS extension modules). In these cases, the AT in the loading module is already "adapted" to the KSq since they are naturally found together. Other examples use a combination of sources to produce the loading module (pPFL35 uses KSq from oleandomycin, AT2 from rapamycin, and ACP from the DEBS loading module to combine to form a "hybrid" loading module to join with DEBS extension modules); in this combination case, a portion of the loading module ***is*** naturally associated with at least the first extension module. In fact, the Examiner can find no examples wherein no portion of the loading module is naturally associated with the first extension module except where the domains of the loading module are all naturally associated with each other.

Dependent Claim 29 (omitted from this rejection) requires the entire loading module be from specific PKSs, like many of the examples in the specification. Clarification of the instant claims is required.

21. (New) Claims 20, 23-25, 30, and 43-53 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In line 19, the phrase "corresponding to" (referring to the natural KSq) is unclear as to its metes and bounds; the Examiner suggests the term ---represents--- for clarity as found in Claim 54.

22. (New) Claims 20, 23-25, 30, and 43-53 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The nature of "a cysteine in the active site" is unclear since "a" indicates more than one while the specification describes only a single, specific cysteine in the active site. To indicate this cysteine, the Examiner suggests ---the cysteine in the active site--- for clarity.

23. (New) Claims 20, 23-25, and 55-56 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The antecedent basis of "the acyltransferase domain" (AT) is unclear since Claims 43 and 54, the parent claims, are drawn to a polyketide synthase that contains a loading module and an extension module, wherein both loading and extension modules contain AT domains. Even though Claims 43 and 54 refer specifically to only the loading module AT, the antecedent basis of "the acyltransferase domain" is unclear. The Examiner suggests ---said acyltransferase domain--- or the acyltransferase domains of the loading module--- for clarity. Clarification is required.

24. (New) Claims 46-53 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "derived from" is unclear as to its metes and bounds. What level of similarity to naturally-occurring type I extension AT domains is required? Clarification is required.

25. (New) Claims 50-51 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "corresponds to" is unclear. Must exactly AT6 of niddamycin by used or can any corresponding/homologous AT domain be used? If the latter is the correct scope, how homologous must the domains be? Clarification is required.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph

26. Previous rejection of Claim 38 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicants' cancellation of said claim.

27. Previous rejection of Claims 17-30 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicants' cancellation and/or amendment of said claims.

New or Maintained - Claim Rejections - 35 U.S.C. § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

28. (New) Claims 25, 49, and 60 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of using ***any*** acyltransferase domain that is specific for ethylmalonyl is not supported in the specification as originally filed. While the

specification describes an ethyl-substituted chain as being incorporated by AT5 of spiramycin and monensin as part of the invention (see page 27), no generic description is provided in the specification as originally filed to support the breadth claimed. Applicants must cite clear support (page and line number) for the alleged new matter or cancel it in response to this Office action.

If Applicants can support the claimed breadth, the instant claims are also rejected under 35 U.S.C. § 112, first paragraph, written description. Unlike malonyl- and methylmalonyl-specific KS domains, ethylmalonyl-specific KS domains are much less well known in the art. While alignments of malonyl- and methylmalonyl-specific KS domains describe the required features of said domains, this is not the case for ethylmalonyl-specific KS domains. Thus, the term ethylmalonyl-specific KS domain is insufficient to provide adequate written description in the absence of a specific structure.

29. (New) Claims 30, 53, and 63 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of a PKS that produces a polyketide having a side chain of an allyl or hydroxymethyl group wherein the PKS does not require a specific structure is not supported in the specification as originally filed. While the specification describes these sides chains as being incorporated specifically by PKSs having, as a part of the loading modules, AT4 of FK506 and AT6 of monensin (see page 27), respectively, no generic description is provided in the specification as originally filed to support the breadth claimed.

Applicants must cite clear support (page and line number) for the alleged new matter or cancel it in response to this Office action.

If Applicants can support the claimed breadth, the instant claims are also rejected under 35 U.S.C. § 112, first paragraph, written description. Unlike malonyl- and methylmalonyl-specific sidechains, allyl and hydroxymethyl sidechains are much less well known in the art. While alignments of PKSs producing polyketides having malonyl- and methylmalonyl-specific sidechains describe the required features of said PKSs, this is not the case for PKSs producing polyketides having allyl and hydroxymethyl sidechains. Thus, the terms allyl and hydroxymethyl sidechains are insufficient to provide adequate written description in the absence of specific structure.

30. (New) Claims 20, 23-25, 29, 30, 43, 44, 53, and 63 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. While numerous examples of hybrid PKSs that produce 14-membered macrolides (specifically erythromycin homologues) are taught in the specification, no specific description of hybrid PKSs that produce 12-membered macrolides is taught. In fact, no mention of naturally-occurring PKSs that produce 12-membered macrolides is found, while 14-membered macrolides oleandomycin and erythrmyocin and 16-membered macrolides tylosin, niddamycin, and spiramycin are taught.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics,

functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not disclose any representative species of the claimed genus. Therefore, Claims 20, 23-25, 29, 30, 43, 44, 53, and 63, as written, fail to satisfy the written description requirement.

31. (New) Claims 20, 23-25, 30, and 43-63 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant invention is drawn to hybrid PKSs having a loading module wherein the domains of the loading module can be from different sources and/or be modified (see 112, 2nd paragraph rejection above as well) wherein the AT domain is "adapted to load" the starter unit onto the KS domain. No description of this adaptation of an AT domain is found for when a KSq domain is not naturally associated with an AT domain.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not identify particular characteristics of AT domains "adapted" to KSq domains. Therefore, Claims 20, 23-25, 30, and 43-63, as written, fail to satisfy the written description requirement.

32. (New) Claims 54-63 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. While numerous examples of hybrid PKSs having naturally-occurring KSq domains are taught in the specification, no specific description of hybrid PKSs having engineered KSq domains is taught. To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not disclose any representative species of the claimed genus. Therefore, Claims 54-63, as written, fail to satisfy the written description requirement.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

33. Previous rejection of Claim 16 under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al.* is withdrawn by virtue of Applicant's cancellation of said claim.

New or Maintained - Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

34. (New) Claims 46, 48, 52, and 53 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al*. (Production of a novel polyketide through the construction of a hybrid polyketide synthase. Gene (1996) 183:231-236). The instant claims are drawn to a hybrid polyketide synthase (PKS) of a loading module and extension modules from different sources wherein the loading module is from tylosin, having methylmalonyl-specificity, and wherein the hybrid PKS produces a 16-membered macrolide with propionate starter units.

Kuhstoss *et al*. teach a hybrid polyketide synthase comprised of the loading module (KS^Q-AT-ACP) of the tylosin PKS and the extension modules of spiramycin PKS (see page 233, left column and Figure 3). The loading module of the tylosin PKS **inherently** has the capacity for loading and decarboxylation as itemized in Claim 46. The tylosin loading module and spiramycin extension modules are not naturally associated with each other. The hybrid PKS produces a 16-membered polyketide (see Figure 3), which production attests to the ability of the loading module to effect loading and decarboxylation. Moreover, this hybrid PKS uses propionate as starter units (see positions 6 and 15 in the ring). The loading module of the tylosin PKS contains a KS^Q domain (a ketosynthase domain having a glutamine, not a cysteine, as an active site residue) and is specific for methylmalonyl-CoA and propionate.

Response to Arguments

35. Anticipating a rejection using Kuhstoss *et al*, Applicants specifically note that Kuhstoss *et al*. does not teach hybrid PKSs that produce 12- or 14-membered polyketides; the Examiner agrees that Kuhstoss *et al*. teach production of 16-membered polyketides. This teaching, however does anticipate Claim 46 and some dependent claims of Claim 46 since Claim 46 is

identical to Claim 43 except for producing any polyketide and not just 12- or 14-membered polyketides (the wherein clause about being derived from any type I PKS extension module is accepted breadth of the term "AT" domain in Claim 43). This Kuhstoss *et al.* rejection has been previously made in prosecution.

Withdrawn - Claim Rejections - 35 U.S.C. § 103

36. Previous rejection of Claims 17-19, 21, 22, 28, and 38-40 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Khosla (Chemical Reviews (1997) 97:2577-2590) is withdrawn by virtue of Applicants' cancellation of said claims.

New or Maintained - Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

37. Previous rejection of Claims 20, 23-25, 29, 30, and 43 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Khosla (Chemical Reviews (1997) 97:2577-2590) is maintained; this rejection is reiterated below to include rejection of newly added claims together in a single rejection. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that no suggestion to combine the references is found. However, the secondary reference is added for several reasons: (1) to provide evidence of the nature of the spiramycin and erythromycin PKS; in this case, no motivation to combine is necessary since the additional reference teaches an inherent feature in the primary reference, (2) to teach the deletion engineered PKS, and (3) to support the reasonable expectation of success for the combinations suggested by Khosla *et al.* (the patent). The combination of reference is obvious because both Khosla *et al.* and Khosla teach the production of novel polyketides using genetic engineering of PKS systems. One would have been motivated to combine said references for the production of novel polyketides as noted throughout both Khosla *et al.* and Khosla.

Applicants argue that Khosla teaches away from combing "inactive" KSq domains; however, Khosla is not used for this combining – Khosla *et al.* (the US patent) alone renders obvious such combinations. Khosla is used in the rejection specifically for the reasons cited above. Thus, Applicants' arguments concerning the teaching away of Khosla are irrelevant.

In further arguments, "Applicants also continue to take exception to the Examiner's unfounded extrapolation of type II polyketide synthases to type I polyketide synthases" due to a comment in Khosla about "a fundamentally new paradigm". It is clear from Figure 4 in Khosla (see page 2580) that modular PKSs, while being a new paradigm, are clearly understood in terms of modules, domains, and activities at the time of the invention. Thus, Khosla *et al.* teach a clear understanding of type I PKSs in combination with the state of the art at the time of the invention.

Any extrapolations and/or "personal knowledge of the Examiner" are omitted from the present rejection; Applicants' arguments in this vein are moot.

Applicants also argue that Khosla *et al.* do not describe any practical way of making the products claimed (and rejected herein). In response, the Examiner notes that splicing of DNA and expression to produce the encoded enzymes is well within the abilities of a skilled artisan at the time of the invention.

For all of the above reasons, the obviousness type rejection using Khosla *et al.* and Khosla is maintained and extrapolated as set forth below.

38. (New/Maintained) Claims 20, 23-25, 29, 30, 43-45, 47, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Khosla (Harnessing the Biosynthetic Potential of Modular Polyketide Synthases. Chemical Reviews (1997) 97:2577-2590). The instant claims are drawn to hybrid PKS enzymes wherein the loading modules use (1) a naturally occurring KSq domain, (2) a malonyl-, methylmalonyl-, or ethylmalonyl-specific AT domain with an active site arginine residue, and (3) an ACP domain, wherein the hybrid PKSs produce 12-, 14-, and 16-membered macrolides. The instant claims are also drawn to hybrid PKSs wherein the loading module is from spiramycin, which loading module is also heterologous to the extension modules.

Khosla *et al.* teach the basic construction of type I (modular) PKS enzymes. Type I PKS enzymes minimally contain a ketosynthase (KS) domain, an acyltransferase (AT) domain, and an acyl carrier protein (ACP) domain (see column 19, lines 12-20). Khosla *et al.* teach hybrid PKS enzymes using a combination of "enzymes, modules, active sites or portions thereof derived from aromatic, modular or fungal PKS gene clusters" (see column 10, lines 40-45). Thus, Khosla *et al.* teach the combination of any of these domains to produce a minimal PKS.

Khosla *et al.* specifically teach optional polyketide gene clusters such as spiramycin (see column 14, line 32), whose loading module naturally contains a KSq domain and whose AT domains naturally use malonyl-CoA or ethylmalonyl (see Khosla as evidence, page 2581, left column). Khosla *et al.* specifically teach optional polyketide gene clusters such as erythromycin (see column 14, line 30), whose AT domains naturally use methylmalonyl-CoA (see Khosla as evidence, page 2580, left column). Khosla *et al.* also specifically teach optional polyketide gene clusters such as monensin (see column 14, line 32), which contains an AT domain with an active site arginine (see instant specification as evidence, page 17).

Khosla *et al.* teach no differentiation between loading module AT domains and other AT domains, thus mixing and matching of all domains is wholly described. While the full extent of the function of KSq domains and their related AT domains in loading modules may have not been appreciated by Khosla *et al.*, this is not necessary to obviate the rejection since the product need only be obvious to make – and not necessarily for the reasons cited in Applicants' arguments.

The polyketides produced by mixing and matching the PKS domains described in Khosla *et al.* minimally mimic those found in the PKS gene clusters described (see column 14, lines 30-33) and include 14- and 16-membered macrolides. Khosla *et al.* do not teach PKSs making 12-membered macrolides.

Khosla teaches 12-membered macrolides by a deletion of erythromycin modules (see page 2586, Figure 10).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to use the teachings of Khosla *et al.* to produce the claimed invention because Khosla *et al.*

describe all possible combinations of genes, modules, domains, and portions thereof. Further, one would have been motivated to add the additional permutation taught by Khosla (the deletion module PKS) as an obvious variation on the theme of making novel polyketides since Khosla describe the deletion experiments as those that "can therefore be used … to produce novel biosynthetic products via genetic engineering" (see page 2586, right column). One would have been motivated to produce such hybrid PKS enzymes because of the great therapeutic potential of novel polyketides that can be easily produced, in combinatorial fashion, using the system of mixing and matching described by Khosla *et al*. One would have had a reasonable expectation of success that such combination of genes, modules, domains, and portions thereof would render functional polyketides due to the extensive similarities among modular and aromatic PKS enzymes (see Khosla).

Summary of Pending Issues

39. The following is a summary of the issues pending in the instant application; each issue must be addressed in a complete response to the instant Office action:

a) The specification stands objected to in its description of the figures.
b) Claims 43, 46, and 54 stand objected to for a typographical error.
c) Claims 20, 23-25, 29, 30, and 43-63 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the generally narrative nature of the claims.
d) Claims 20, 23-25, 29, 30, and 43-63 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the use of the term "residue".
e) Claims 20, 23-25, 30, and 43-63 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the nature of the loading module.
f) Claims 20, 23-25, 30, and 43-53 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "corresponding to" (referring to the natural KSq).
g) Claims 20, 23-25, and 55-56 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the antecedent basis of "the acyltransferase domain" (AT).
h) Claims 46-53 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "derived from".

i) Claims 50-51 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "corresponds to".
j) Claims 25, 49, and 60 stand rejected under 35 U.S.C. § 112, first paragraph, new matter/written description, for ethylmalonyl AT domains.
k) Claims 30, 53, and 63 stand rejected under 35 U.S.C. § 112, first paragraph, new matter/written description, for PKS that produces a polyketide having a side chain of an allyl or hydroxymethyl group.
l) Claims 20, 23-25, 29, 30, 43, 44, 53, and 63 stand rejected under 35 U.S.C. § 112, first paragraph, written description, for PKSs producing 12-membered macrolides.
m) Claims 20, 23-25, 30, and 43-63 stand rejected under 35 U.S.C. § 112, first paragraph, written description, for PKSs with adapted AT domains wherein the AT and the KSq are not naturally associated.
n) Claims 54-63 stand rejected under 35 U.S.C. § 112, first paragraph, written description, for PKSs with engineered KSq domains.
o) Claims 46, 48, 52, and 53 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al*.
p) Claims 20, 23-25, 29, 30, 43-45, 47, and 49 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Khosla *et al*. (USPN 5,712,146) in view of Khosla (Harnessing the Biosynthetic Potential of Modular Polyketide Synthases. Chemical Reviews (1997) 97:2577-2590).

Allowable Subject Matter

40. The Examiner notes that Claims 50, 51, 61, and 62 are considered free of the prior art. These claims are drawn to specific species of the genus of hybrid PKSs. Claims 50 and 61 require the AT of module 6 of the niddamycin PKS, and Claims 51 and 62 require the AT of module 4 of the FK506 PKS. Such exact combinations in the hybrid PKSs cannot specifically be rendered obvious by Khosla *et al*. (USPN 5,712,146).

The Examiner also notes that the closest prior art is Marsden *et al*. who teach the combination of the loading module of the avermectin PKS and the extension modules of the erythromycin PKS. The hybrid PKS of Marsden *et al*. produces a 14-membered macrolide, such as in the "proviso" statement in Claims 43, 46, and 54.

Conclusion

41. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. The instant Office action is **non-final** due to new grounds of rejection set forth herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Kathleen M Kerr
Examiner
Art Unit 1652

December 10, 2003